

IN THE CLAIMS:

Please cancel claim 1 without prejudice.

Please add the following new claims:

- Sub E2*
- 2. An isolated zinc finger-nucleotide binding polypeptide variant comprising at least two zinc finger modules wherein the amino acid sequence of at least one zinc finger module of said variant has at least one amino acid sequence modification.
- Sub C1*
3. The variant of claim 2, which is derived from a zinc finger-nucleotide binding polypeptide selected from the group consisting of Zif268 and TFIIIA.
4. The variant of claim 2, wherein the polypeptide contains a linker region between zinc finger modules, the linker comprising the amino acid sequence TGEKP.
5. The variant of claim 2, wherein the zinc finger binding polypeptide variant is a truncated zinc finger protein.
- B1*
6. A nucleotide sequence encoding a zinc finger-nucleotide binding polypeptide variant of claim 2.
7. A recombinant expression vector containing the zinc finger-nucleotide binding polypeptide variant of claim 2.
- C*
8. An in vitro method for inhibiting a transcriptional function of a target cellular nucleotide sequence comprising a zinc finger-nucleotide binding motif, the method comprising contacting the motif with an effective amount of a zinc finger-nucleotide binding polypeptide variant of claim 2, wherein the variant binds to the target cellular nucleotide sequence.

9. The method of claim 8, wherein the zinc finger binding polypeptide variant is a truncated zinc finger protein.
10. The method of claim 8, wherein the cellular nucleotide sequence is DNA.
11. The method of claim 8, wherein the cellular nucleotide sequence is RNA.
12. The method of claim 8, wherein the cellular nucleotide sequence is a structural gene nucleotide sequence.
13. The method of claim 8, wherein the cellular nucleotide sequence is a promoter nucleotide sequence.
14. The method of claim 8, wherein the cellular nucleotide sequence is an oncogene nucleotide sequence.
15. The method of claim 8, wherein the cellular nucleotide sequence is a plant cellular nucleotide sequence.
16. The isolated zinc finger-nucleotide binding polypeptide variant of claim 2, comprising at least three zinc finger modules wherein at least one module binds to a cellular nucleotide sequence.
17. The isolated zinc finger-nucleotide binding polypeptide variant of claim 2, comprising at least five zinc finger modules wherein at least one module binds to a cellular nucleotide sequence.
18. The isolated zinc finger-nucleotide binding polypeptide variant of claim 2, wherein the polypeptide binds to a cellular nucleotide sequence having 18 contiguous base pairs.

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SUB E3

19. The isolated zinc finger-nucleotide binding polypeptide variant of claim 2, wherein the polypeptide binds to a cellular nucleotide sequence comprising two 9-base pair binding sites.
20. The nucleotide sequence of claim 6, further comprising a nucleotide sequence encoding a transcriptional activation domain in operable linkage with the nucleotide sequence encoding the zinc finger-nucleotide binding polypeptide variant.
21. A nucleotide sequence encoding a zinc finger-nucleotide binding polypeptide variant having zinc finger modules that bind to a target cellular nucleotide sequence, wherein at least one zinc finger module that binds a target cellular nucleotide sequence is modified, comprising a nucleotide sequence encoding a transcriptional activation domain in operable linkage with the nucleotide sequence encoding the zinc finger-nucleotide binding polypeptide variant.
22. The nucleotide sequence of claim 21, wherein the transcriptional activation domain is a herpes simplex virus VP16 protein or functional fragments thereof.
23. The nucleotide sequence of claim 6, further comprising a nucleotide sequence encoding a repressor domain in operable linkage with the nucleotide sequence encoding the zinc finger-nucleotide binding polypeptide variant.
24. A nucleotide sequence encoding a zinc finger-nucleotide binding polypeptide variant having at least one zinc finger module that binds to a target cellular nucleotide sequence and is modified comprising a nucleotide sequence encoding a repressor domain in operable linkage with the nucleotide sequence.
25. The nucleotide sequence of claim 24, wherein the repressor domain is the Kruppel-associated box A domain (KRAB-A) or functional fragments thereof.

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26. The method of claim 8, wherein the variant is derived from a zinc finger-nucleotide binding polypeptide selected from the group consisting of Zif268 and TFIIIA.

27. A method for isolating a zinc finger-nucleotide binding polypeptide variant which binds to a cellular nucleotide sequence comprising:

- a) identifying the amino acids in a zinc finger-nucleotide binding polypeptide that bind to a first cellular nucleotide sequence and modulate the function of the nucleotide sequence;
- b) creating an expression library encoding the polypeptide variant containing randomized substitution of the amino acids identified in step a) above;
- c) expressing the library in a suitable host cell; and
- d) isolating a clone that produces a polypeptide variant that binds to a second cellular nucleotide sequence and modulates the function of the second nucleotide sequence,

wherein the variant is comprised of at least two zinc finger modules and wherein the amino acid sequence of at least one module that binds the second nucleotide sequence comprises two cysteines and two histidines whereby both cysteines are amino proximal to both histidines and wherein at least one of the at least two modules of said variant has at least one amino acid sequence modification.

28. The method of claim 27, wherein the library is expressed in a phage surface expression system.

29. The method of claim 28, wherein the phage expression system includes a reducing reagent which allows folding of expression products on the phage surface.

30. The method of claim 29, wherein the reducing reagent is dithiothreitol.

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31. The method of claim 27, wherein the library is randomized by PCR using primers containing degenerate triplet codons at sequence locations corresponding to the determined amino acids.
32. The method of claim 27, wherein the variant is derived from a zinc finger-nucleotide binding polypeptide selected from the group consisting of Zif268 and TFIIIA.
33. The method of claim 32, wherein the variant derived from the zinc finger-nucleotide binding polypeptide Zif268 is modified at any of residues 1, 3, 4, 5, 6 or 7, or any combination thereof, as set forth in SEQ ID NO:14.
34. The method of claim 32, wherein the variant derived from the zinc finger-nucleotide binding polypeptide Zif268 is modified at any of residues 1, 2, 3, 4, 5 or 6, or any combination thereof, as set forth in SEQ ID NO:15.
35. The method of claim 32, wherein the variant derived from the zinc finger-nucleotide binding polypeptide Zif268 is modified at any of residues 1, 3, 4, 5, 6 or 7, or any combination thereof, as set forth in SEQ ID NO:5.
36. The method of claim 27, wherein the modulation of function is enhancement of transcription of a gene operatively linked to the cellular nucleotide sequence.
37. The method of claim 27, wherein the modulation of function is suppression of transcription of a gene operatively linked to the cellular nucleotide sequence.
38. The method of claim 27, wherein the cellular nucleotide sequence is DNA.
39. The method of claim 27, wherein the cellular nucleotide sequence is RNA.

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cont.